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Report

Pharmaceutical Evaluation of Tablet Splitting and Crushing of Imeglimin Hydrochloride Tablets: An In Vitro Dissolution Study

Atsushi Ishimura,^{a,*} Hina Fujikura,^a and Motoki Inoue^b

^aLaboratory of Clinical Pharmacy Assessment, Hoshi University, 2-4-41 Ebara, Shinagawa-ku, Tokyo 142-8501, Japan;

^bDepartment of Physical Chemistry, Hoshi University, 2-4-41 Ebara, Shinagawa-ku, Tokyo 142-8501, Japan

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Imeglimin hydrochloride is a novel oral antidiabetic agent used to treat type 2 diabetes mellitus. Tablet splitting and crushing are occasionally required in clinical practice to facilitate medication administration; however, their effects on the pharmaceutical performance of imeglimin tablets remain unclear. This study evaluated the effects of tablet splitting and crushing on the *in vitro* dissolution characteristics of imeglimin hydrochloride tablets. Dissolution testing was performed using intact, halved (0.5 tablet $\times$ 2), and crushed 500 mg tablets under conditions consistent with the Japanese Pharmacopoeia. The paddle method (50 rpm, 900 mL, $37.0 \pm 0.5^\circ\text{C}$) was used with the first fluid (pH 1.2), the second fluid (pH 6.8), and purified water. Samples were collected at 5, 10, 15, 30, and 45 min, and imeglimin concentrations were determined spectrophotometrically at 245 nm. All experiments were performed in quintuplicate. Crushed tablets showed significantly higher percentages dissolved than intact and halved tablets at 5 and 10 min in all dissolution media. However, the dissolution profiles converged over time, and all preparations achieved nearly complete drug dissolution within 30 min under all test conditions. The powder weight recovery after crushing was $98.7 \pm 1.5\%$, indicating that the physical loss of tablet material during the crushing and recovery procedures was small. These findings indicate that tablet crushing significantly increased the percentage dissolved during the early phase of dissolution but did not affect the final extent of dissolution under the experimental conditions used. Further studies should evaluate the effects of tablet manipulation on pharmacokinetics and clinical outcomes.

Key words imeglimin, dosage-form modification, dissolution test

INTRODUCTION

Imeglimin hydrochloride (Twymee[®]) is the first agent of a new class of oral antidiabetic drugs that improves mitochondrial bioenergetics and exerts glucose-lowering effects through dual actions on insulin secretion and insulin sensitivity. Since its approval in Japan in 2021, imeglimin's clinical use has steadily increased.^{1,2)} A recent nationwide database study demonstrated expanding utilization of imeglimin among patients with type 2 diabetes mellitus, particularly in older adults, highlighting the growing need for practical pharmaceutical information regarding its appropriate administration.³⁾

Appropriate administration of oral medications is essential for maintaining therapeutic efficacy. In routine clinical practice, tablet splitting and crushing are frequently performed for patients who have difficulty swallowing large tablets, require individualized medication administration, or receive enteral nutrition.⁴⁾ Although such dosage-form modifications are often unavoidable, inappropriate tablet manipulation may alter dose recovery, dissolution characteristics, and bioavailability, potentially affecting therapeutic efficacy and safety. Fur-

thermore, despite the widespread use of tablet manipulation in hospitals and long-term care facilities, pharmaceutical evidence supporting these practices remains limited for many oral medications, particularly newly introduced drugs. Therefore, pharmaceutical evaluation of manipulated tablets is essential to ensure that dosage-form modification does not compromise pharmaceutical quality or drug performance.

Twymee[®] 500 mg is a film-coated tablet measuring 17.6 mm in length, 7.1 mm in width, and 5.3 mm in thickness and weighing approximately 569 mg.⁵⁾ Tablet size is an important factor affecting the acceptability of oral medications, particularly in older patients and those with swallowing difficulties. A previous study evaluating medicine acceptability in older patients demonstrated that tablet size was associated with acceptability, with smaller tablets being better accepted among patients with swallowing disorders.⁶⁾ Given its relatively large dimensions, Twymee[®] 500 mg may therefore be difficult to swallow for some patients, particularly those with impaired swallowing function. Although tablet splitting or crushing may facilitate administration in clinical practice, information regarding the pharmaceutical properties of imeglimin tablets

*To whom correspondence should be addressed. e-mail: ishimura.atsushi@hoshi.ac.jp



following such dosage-form modifications remains limited. To our knowledge, no previous study has evaluated the effects of tablet splitting or crushing on the dissolution characteristics of imeglimin hydrochloride tablets.

Dissolution testing is widely used to evaluate the pharmaceutical performance of immediate-release oral dosage forms and to determine whether physical manipulation affects drug release characteristics. Because dissolution behavior is a key indicator of pharmaceutical quality, dissolution testing provides useful evidence for health care professionals when dosage-form modification cannot be avoided during routine medication management.⁷⁾

Therefore, the present study evaluated the dissolution characteristics of intact, halved, and crushed imeglimin hydrochloride tablets under Japanese Pharmacopoeia dissolution conditions. In addition, powder weight recovery after tablet crushing was assessed to determine whether tablet manipulation affects the pharmaceutical quality of imeglimin hydrochloride tablets.

MATERIALS AND METHODS

Test preparations Imeglimin hydrochloride 500 mg tablets (Twymeg® Tablets 500 mg; lot No. 77110) were used, and their dissolution characteristics were evaluated under three preparation conditions: (1) intact (one 500 mg tablet), (2) halved (two halves obtained from one tablet; 0.5 tablet $\times$ 2), and (3) crushed, prepared from one intact tablet. Tablet splitting was performed along the longitudinal axis using a commercially available tablet cutter (Okusuri Chokkin® HC-100, Daido Chemical Industry Co., Ltd., Osaka, Japan). For the crushed-tablet preparation, the entire tablet, including the film coating, was manually crushed using a mortar and pestle without removal of the coating. Because crushing was performed manually, a fixed crushing speed was not defined, and neither crushing time nor force was standardized. To evaluate powder weight recovery during crushing, the recovered powder was weighed after each crushing, and the powder weight recovery (%) was calculated by dividing the recovered powder weight by the initial tablet weight and multiplying by 100.

Dissolution Test Dissolution testing was conducted under conditions consistent with the Dissolution Test described in the General Tests of the Japanese Pharmacopoeia, Nineteenth Edition. The dissolution media consisted of the first fluid (pH 1.2) and second fluid (pH 6.8) for dissolution testing (FUJIFILM Wako Pure Chemical Corporation, Osaka, Japan) and purified water (Yamato Scientific Co., Ltd., Tokyo, Japan). The dissolution medium volume was 900 mL. The temperature was maintained at $37.0 \pm 0.5^\circ\text{C}$. A dissolution tester (NTR-3000, Toyama Sangyo Co., Ltd., Osaka, Japan) equipped with a paddle apparatus was operated at a rotation speed of 50 rpm. For each dissolution medium, intact, halved, and crushed tablets were tested in quintuplicate ($n = 5$). The time at which the tablet preparation was introduced into the dissolution medium was defined as 0 min. Samples were collected at 5, 10, 15, 30, and 45 min after the start of the dissolution test, with 5 min being the first sampling time point. At each sampling time point, 5 mL of dissolution medium was withdrawn and replaced with an equal volume of fresh medium maintained at the same temperature. Imeglimin concentrations were determined spectrophotometrically. After appropriate dilution, absorbance was measured at 245 nm using a UV-visible spectrophotometer

(ASUV-1100, As One Corporation, Osaka, Japan). Reference solutions corresponding to 0%, 20%, 40%, 50%, 60%, 80%, and 100% of the labeled drug content were prepared for each dissolution medium and measured under the same conditions. The percentage dissolved was determined from the measured absorbance using linear interpolation between adjacent reference concentrations. Blank correction was performed using the corresponding dissolution medium. Values were not truncated at 100%.

Statistical Analysis Differences in the percentage dissolved among intact, halved, and crushed tablets during the initial phase of dissolution (5, 10, and 15 min) were evaluated separately for each dissolution medium using one-way analysis of variance (ANOVA), followed by Tukey's multiple-comparison test. A two-sided p value < 0.05 was considered statistically significant.

RESULTS

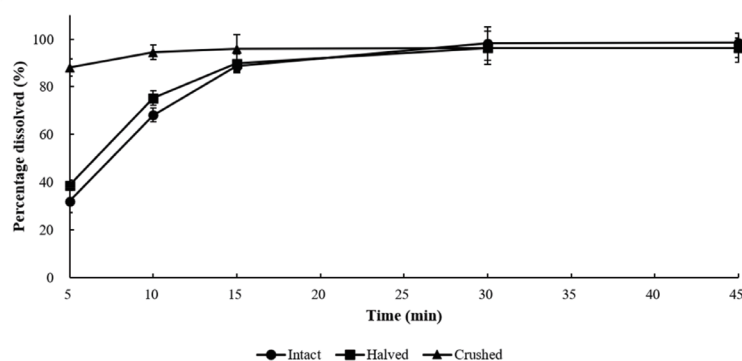
In the first dissolution medium (pH 1.2), the percentage dissolved from crushed tablets was significantly higher than that from both intact and halved tablets at 5 and 10 min (Tukey's test, $p < 0.001$ for all comparisons). At 15 min, the percentage dissolved from crushed tablets remained significantly higher than that from intact tablets ($p = 0.026$), whereas the difference between crushed and halved tablets was not statistically significant ($p = 0.065$). In the second dissolution medium (pH 6.8), the percentage dissolved from crushed tablets was also significantly higher than that from both intact and halved tablets at 5 and 10 min ($p < 0.001$ for all comparisons). At 15 min, crushed tablets showed a significantly higher percentage dissolved than intact tablets ($p = 0.002$), whereas the difference from halved tablets was not statistically significant ($p = 0.083$). In purified water, the percentage dissolved from crushed tablets was significantly higher than that from both intact and halved tablets at 5, 10, and 15 min ($p < 0.001$ for all comparisons). Nevertheless, the dissolution profiles converged over time, and all preparations achieved nearly complete dissolution within 30 min under all test conditions (Fig. 1). The powder weight recovery after crushing was $98.7 \pm 1.5\%$, indicating that the physical loss of tablet material during the crushing and recovery procedures was small.

DISCUSSION

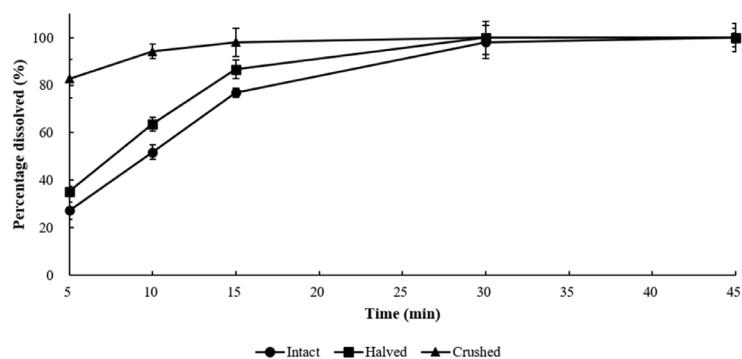
The present study demonstrated that crushed imeglimin hydrochloride tablets exhibited significantly higher percentages dissolved than intact and halved tablets at 5 and 10 min in all dissolution media. Although some differences remained at 15 min, the dissolution profiles subsequently converged, and all preparations achieved nearly complete drug dissolution within 30 min regardless of the dissolution medium.

The accelerated initial dissolution observed for crushed tablets may be related to the increased surface area resulting from tablet crushing. In general, a reduction in particle size increases the surface area available for wetting and dissolution of immediate-release formulations.⁸⁾ However, the particle size distribution of the crushed tablets was not measured in the present study; therefore, the relationship between particle size and the observed dissolution behavior could not be directly evaluated. These findings suggest that tablet crushing accelerated the initial dissolution process, whereas tablet

(A) The first dissolution medium (pH 1.2)



(B) The second dissolution medium (pH 6.8)



(C) Purified water

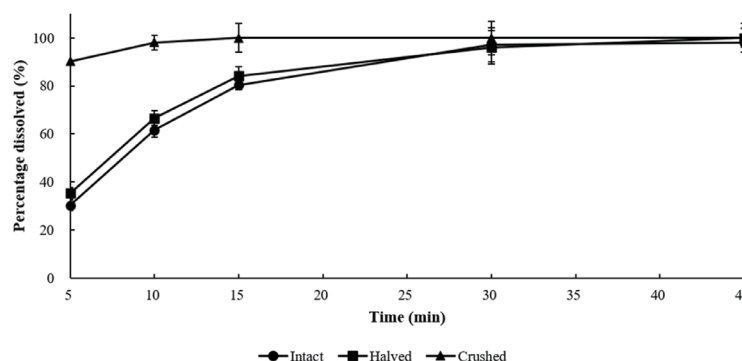


Fig. 1. Dissolution Profiles of Intact, Halved, and Crushed Imeglimin Hydrochloride Tablets in (A) the first dissolution medium (pH 1.2), (B) the second dissolution medium (pH 6.8), and (C) purified water.

Data are presented as the mean $\pm$ standard deviation (SD) ($n = 5$). Statistical comparisons among intact, halved, and crushed tablets at 5, 10, and 15 min were performed using one-way ANOVA followed by Tukey's multiple-comparison test.

splitting had little effect on the dissolution profile, and neither manipulation affected the final extent of dissolution under the experimental conditions used. However, the pharmacokinetic significance of the accelerated initial dissolution observed after crushing remains uncertain. Imeglimin is a small cationic compound with intermediate intestinal permeability, and its intestinal absorption involves both active transport and passive paracellular pathways. Absorption has been reported to decrease with increasing dose, possibly because of saturation of active transport.⁹ In healthy Japanese subjects, imeglimin was readily absorbed, with a median time to maximum plasma concentration (T_{max}) of approximately 1.5-3 h, while the mean elimination half-life ranged from 4.45 to 12.0 h.¹⁰ In the present study, even intact tablets achieved nearly com-

plete dissolution within 30 min under all tested conditions. Considering these absorption and pharmacokinetic characteristics, the differences in dissolution observed during the first 5-15 min may not necessarily translate directly into clinically meaningful differences in systemic exposure. Nevertheless, because the present study evaluated only *in vitro* dissolution, it remains unknown whether crushing affects the rate or extent of imeglimin absorption. Pharmacokinetic studies comparing intact and crushed tablets are therefore required to determine whether the observed differences in early dissolution influence C_{max} , T_{max} , or systemic exposure.

The effect of tablet crushing on drug dissolution may vary depending on the formulation design and physicochemical properties of the drug. Previous studies have shown that crush-

ing can substantially alter the dissolution characteristics of modified-release formulations. For example, Kir *et al.* reported that crushing modified-release metoprolol succinate tablets using a mortar and pestle altered particle size and surface morphology and resulted in dissolution profiles that differed from those of intact tablets.¹¹⁾ These effects were attributed to disruption of the formulation structure responsible for controlling drug release. In contrast, the imeglimin tablet evaluated in the present study is a film-coated tablet, and crushing primarily affected the early phase of dissolution, whereas the dissolution profiles subsequently converged and all preparations achieved nearly complete dissolution within 30 min. These findings suggest that the pharmaceutical consequences of tablet crushing depend on formulation characteristics and that the effect observed with imeglimin should not be generalized to formulations with different drug-release mechanisms.

Tablet manipulation is frequently unavoidable in routine clinical practice, particularly for patients who experience swallowing difficulties, require enteral administration, or have difficulty handling relatively large tablets.⁴⁾ However, physical modification of tablets may alter dose uniformity, powder weight recovery, dissolution characteristics, and ultimately pharmaceutical quality. Therefore, evaluating pharmaceutical performance following tablet manipulation is important before such practices can be considered acceptable. The high powder weight recovery after crushing (98.7%) indicated that the physical loss of tablet material during the crushing and recovery procedures was small. However, because recovery was assessed gravimetrically rather than by quantitative determination of imeglimin content, this finding does not directly demonstrate recovery of the active pharmaceutical ingredient. Although crushing altered the initial dissolution profile, all preparations achieved nearly complete dissolution within 30 min.

Recent real-world evidence has demonstrated the increasing clinical use of imeglimin in Japan, particularly among older adults with type 2 diabetes mellitus.³⁾ As the number of patients receiving imeglimin continues to increase, practical pharmaceutical information regarding tablet manipulation has become increasingly important. The present study complements previous clinical evidence by providing the first pharmaceutical evaluation of tablet splitting and crushing of imeglimin hydrochloride tablets. Nevertheless, these results should not be interpreted as evidence of therapeutic equivalence following tablet manipulation. Because the present investigation was limited to an *in vitro* pharmaceutical evaluation, additional studies are required to determine whether tablet splitting or crushing influences pharmacokinetic characteristics, bioavailability, or clinical outcomes under actual clinical conditions.

Several limitations should be acknowledged. First, this study evaluated only one manufacturing lot of imeglimin tablets. Second, the particle size distribution of the crushed tablets was not evaluated, and crushing was performed manually using a mortar and pestle. Because particle size may vary depending on the crushing method, force, duration, and operator technique, the relationship between crushing conditions, particle size, and dissolution behavior could not be quantitatively assessed. Third, only dissolution behavior and powder weight recovery were investigated, whereas the stability of crushed tablets under one-dose packaging or suspension conditions was not examined. In addition, recovery after crushing was assessed based on powder weight rather than quantitative determination of imeglimin content; therefore, recovery of the

active pharmaceutical ingredient could not be directly evaluated. Finally, the study did not evaluate pharmacokinetic or clinical outcomes following tablet manipulation. Further studies using standardized crushing conditions, quantitative particle-size and drug-content analyses, and commercially available tablet-crushing devices, as well as investigations of pharmacokinetic and clinical outcomes, would provide more comprehensive evidence regarding the pharmaceutical and clinical suitability of dosage-form modification.

In conclusion, tablet crushing significantly increased the percentage dissolved during the early phase of dissolution, particularly at 5 and 10 min, whereas tablet splitting had little effect on the dissolution profile. Neither manipulation affected the final extent of dissolution under the experimental conditions used. These findings provide pharmaceutical information regarding the effects of tablet manipulation on imeglimin hydrochloride tablets.

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Conflict of interest The authors declare no conflict of interest.

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